Tenoxicam compared with diclofenac in patients with ankylosing spondylitis

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Summary

A randomized study was performed on 24 patients with ankylosing spondylitis to compare the efficacy and tolerability of 20 mg tenoxicam daily with 50 mg diclofenac twice daily. There were 6 withdrawals from the group taking tenoxicam and 4 from the diclofenac group. Depression in 1 patient taking tenoxicam was the only significant adverse event. Both drugs were otherwise well tolerated. Tenoxicam and diclofenac were rated as good or excellent by 27% and 55% of patients, respectively. Global assessment, pain and duration of morning stiffness were improved with both drugs but this improvement was not statistically significant and there was no statistically significant difference between the two groups. This study confirms that tenoxicam is effective and well tolerated but larger numbers would be required to detect a small difference between groups.

Key words: Tenoxicam — diclofenac — analgesics, anti-inflammatory — spondylitis, ankylosing

Introduction

Tenoxicam is a new non-steroidal anti-inflammatory drug belonging to the oxicam group. It has a long plasma half-life of 70 to 90 hours allowing for once-daily administration. It is highly protein bound with an unbound fraction in the circulation of only 0.8%.[11] The drug enters the systemic circulation unchanged after oral administration with peak concentrations occurring 0.5 to 1.7 hours after oral administration.[11] Its linear kinetics are the same as those of the other oxicam drugs and studies have shown that dosage changes are unnecessary in renal insufficiency[12] and in the elderly.[3] Tenoxicam is as effective as piroxicam in animal models of inflammation.[6] The exact mechanism of action of tenoxicam

is not certain, although inhibition of prostaglandin synthesis and a decrease in leucocyte accumulation at sites of injury are thought to play a role. Clinical trials have shown tenoxicam to be of benefit in osteoarthritis,[9,14,18] rheumatoid arthritis[2,4,8-10,17] and ankylosing spondylitis.[1,5,15,16]

Diclofenac is a sodium salt of an aminophenylacetic acid and shows potent anti-inflammatory, analgesic, and antipyretic activity in various animal models. Clinical trials in patients with osteoarthritis, rheumatoid arthritis and ankylosing spondylitis have shown it to be better than placebo. Also, it is comparable to indomethacin, ibuprofen and naproxen in rheumatoid arthritis and osteoarthritis and comparable to phenylbutazone in rheumatoid arthritis and to aspirin in osteoarthritis. Trials in patients with ankylosing spondylitis have shown that diclofenac is comparable to indomethacin and phenylbutazone although there are conflicting data from comparative trials with sulindac.[13]

In this randomized study, tenoxicam is compared with diclofenac in patients with ankylosing spondylitis.

Patients and methods

The study was designed as a randomized comparative trial of 20 mg tenoxicam daily and 50 mg diclofenac twice daily over a treatment period of 12 weeks. Inclusion criteria for this study were age between 16 and 65 years and a diagnosis of definite or probable ankylosing spondylitis according to the New York criteria (1966). The exclusion criteria were patients with: spinal arthritis showing active peripheral manifestations (articular or not); spinal arthritis secondary to an intestinal lesion or Behçet's syndrome; disc lesions in spinal arthritis; ulcers or severe organic disease, e.g. hepatic, cardiac or cerebral disease; known intolerance to other non-steroidal anti-inflammatory drugs; current treatment with anticoagulants; and patients treated within the previous 2 months with radiotherapy, thorium, gold, immunosuppressives or steroids.

Patients considered suitable for the study entered a 3-day washout period when usual non-steroidal anti-inflammatory drug therapy was ceased. Only patients noticing an increase in back pain and stiffness were allocated to treatment. Twenty-four patients were randomly allocated to the two treatments, 12 to each group.

Patients were assessed prior to commencement and at 2, 4, 6, 8, and 12 weeks after the start of treatment. Clinical parameters measured included blood pressure (mmHg), diurnal and nocturnal lumbosacral pain and mobility pain (scored 0 = none, 1 = mild, 2 = moderate, and 3 = severe), duration of morning stiffness (minutes), hand-floor distance (cms) and Schoeber's index (cm). At the end of the 12-week period, a global assessment was made of response to treatment by the investigator and patient (scored 0 = symptoms disappeared, 1 = marked decrease in signs/discomfort, 2 = moderate decrease in signs/discomfort, 3 = slight decrease in signs/discomfort, 4 = no change, and 5 = exacerbation of signs/discomfort). Laboratory parameters including full blood count, erythrocyte sedimentation rate, electrolytes, urea, creatinine, glucose and liver function tests were recorded at each assessment and urinalysis was also performed at baseline and 12 weeks.

Statistical analysis

The data entry and statistical analysis was carried out using SPSS/PC+ (Norusis, 1986) and GLIM 3.77 (NAG, 1986). The statistical methods included the unpaired t-test and the Mann-Whitney test for comparison of the drug groups for continuous measures. Fisher's exact test was used for comparing the drug groups for categorical measures. For ordered categorical measures, an exact probability test for a difference in trend across the ordered variable between the two drugs was performed.

Paired t-tests and sign tests were used to analyze differences from the baseline measurements within each drug group. The sign test yields an exact p-value. Differences in efficacy between the two treatments were assessed using Fisher's exact test.

Results

Twelve patients were allocated to each therapy. The mean age was 42 years in the tenoxicam group and 40 years in the diclofenac group. All 12 patients taking tenoxicam were male while 3 of the 12 patients on diclofenac were female. The two groups were equally matched in terms of demographic characteristics, initial disease severity and laboratory measures (Table I). Six of the 12 patients receiving tenoxicam withdrew from the study, 4 due to inefficacy and 2 because they failed to complete treatment. Four of the 12 patients receiving diclofenac withdrew from the study, 3 patients because of inefficacy and 1 before starting her treatment. The difference in the rates of withdrawal from the study for the two groups was not statistically significant.

Table I. Characteristics on entry of patients studied: mean values

Patients	Tenoxicam	Diclofenac
No. studied	12	12
Sex: Male	12	9
Female		3
Age (years)	42	40
Duration of disease (years)	9	7
Duration of stiffness (min)	30	60
Erythrocyte sedimentation rate (mm/hr)	18	27
Haemoglobin (g/dl)	13.9	13.7
Platelets ($\times 10^9$/l)	270	343

There was only one significant adverse event recorded resulting in withdrawal. This patient suffered from depression which was thought to be unrelated to the treatment.

There was no change in haematological parameters during the study. Minor elevations in SGPT were found for 3 patients receiving diclofenac but these had resolved by Week 12 despite continuing treatment.

Efficacy

Table II shows the changes in clinical parameters over the 12-week treatment period. The clinical efficacy was rated as 'good or excellent' by 27% of the patients on tenoxicam and by 55% of patients on diclofenac. Both tenoxicam and diclofenac were associated with improvement in global assessment, pain and duration of morning stiffness but none of these observed differences was statistically significant. There were no statistically significant differences between the two groups for these parameters.

Table II. Changes from baseline (Week 0) in clinical assessments at the end of the trial period (Week 12): mean (±S.D.) values

Assessment	Tenoxicam	Diclofenac
Diurnal pain		
Week 0	1.8±0.8	1.8±0.8
Week 12	1.3±0.8	0.9±0.6
Nocturnal pain		
Week 0	2.2±0.9	2.1±0.8
Week 12	1.3±1.2	1.0±0.8
Mobility pain		
Week 0	1.7±0.9	1.4±1.2
Week 12	1.8±0.8	1.0±0.8
Hand-to-floor distance (cm)		
Week 0	23.7±16.3	19.6±16.9
Week 12	16.8±15.9	19.0±17.6
Schoeber's index (cm)		
Week 0	2.6±1.2	2.4±2.0
Week 12	4.2±1.8	2.4±2.3
*Morning stiffness (min)**		
Week 0	30 (10 to 180)	60 (0 to 1440)
Week 12	15 (0 to 20)	3 (0 to 15)
Global assessment (Week 12)		
Investigators	2.5±2.1	2.4±1.2
Patients	2.3±2.0	1.6±1.2

*median values (95% confidence limits)

The physician's overall assessment of treatment combined an assessment of both tolerance and efficacy. There was no statistically significant difference in the distribution of the ratings between the two drugs. The overall assessment score was 2.9 for tenoxicam and 2.5 for diclofenac (score: 1=excellent; 2=good; 3=moderate; 4=bad).

Discussion

Ankylosing spondylitis is a chronic inflammatory disorder mainly affecting the spine and sacro-iliac joints resulting in pain and stiffness. The primary pathological site is the insertion of ligaments and capsules into bone (the enthesis). The inflammatory process eventually results in ossification in the region of the discs, apophyseal and sacro-iliac joints as well as the entheses. A peripheral arthritis may also occur. The mainstay of treatment is exercise combined with a non-steroidal

anti-inflammatory drug. The purpose of the anti-inflammatory medication is to enable the patient to carry out an adequate exercise programme, to maintain good posture, and to follow normal activities.[7]

Several studies have shown that tenoxicam is effective in the treatment of ankylosing spondylitis. In an open study[15] in which 21 patients were treated for 6 weeks there was significant improvement in most patients in terms of morning stiffness, lumbosacral pain, pain on movement, maximum tolerated period of immobility in a sitting position, hand-floor distance and the Schoeber index. The only adverse effect was dyspepsia in 1 patient. Two studies[1,5] have demonstrated that tenoxicam is comparable to piroxicam and one study[16] that it was more effective and faster in onset of action than piroxicam. Our study is the first to compare tenoxicam with diclofenac.

Unfortunately, the numbers in our study were small, meaning that statistical significance is unlikely even for highly efficacious treatments. However, both drugs demonstrated improvements in terms of clinical efficacy, patient and investigator global assessment, lumbosacral pain and duration of morning stiffness, although these changes were not statistically significant. The only parameter in which there was no improvement was mobility pain in the tenoxicam group. To obtain a difference of 25% between treatment groups with a power of 80% at the 5% level, at least 250 patients would be required in each group. To achieve this would require a very prolonged, multi-centre study.

The only adverse event that occurred was depression and it is unlikely that this was caused by the tenoxicam. The excellent tolerance of this drug and its demonstrated efficacy in this study makes it a reasonable therapeutic option in patients with ankylosing spondylitis.

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